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Pharmacokinetic modeling as a tool for biological monitoring

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Summary. The relationships between biological indicators and exposure or tissue burdens are determined by the pharmacokinetic behaviour of the chemical. They can be studied by pharmacokinetic models of various types. Simple pharmacokinetic models are used here to describe general relationships valid for large groups of chemicals or situations. Important parameters to consider are the half-life of the biological indicator, the individual variability and the exposure variability. Biological sampling strategies are presented for monitoring of groups of workers, or individual workers. For specific chemicals, mainly solvents, more elaborate models can be developed, i.e., physiologically-based pharmacokinetic models including physiological, metabolic and physico-chemical parameters. Such models are useful to describe the influence of confounding factors. Physiologically-based pharmacokinetic models can also be developed for metals and metalloids. Antimony is presented here as an example. In conclusion, pharmacokinetic modeling brings much information on sampling time, sample size, limit values, effect of physical workload and of individual physiological parameters.

Key words: Biological monitoring — Pharmacokinetic modeling — Statistics — Half-life

Introduction

The use of biological monitoring to assess occupational exposure is complicated by the variability in biological levels of chemicals which can be observed both as a function of time, and at a given time between individuals. Fig. 1 presents the kinetic behavior of 2 hypothetical biological indicators in 3 situations: a constant steady exposure, a constant industrial exposure and a fluctuating industrial exposure (Droz and Wu 1991). Biological levels are largely influenced by exposure conditions and their relationship to exposure is not univocal. In a real situation, biological variability would still make the situation less evident, due to both within a worker and between workers differences.

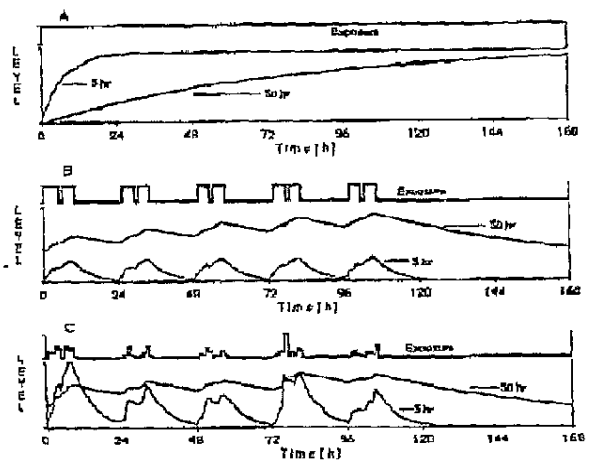

Fig. 1. Biological indicators with half-lives of 5 and 50 h in 3 situations: (A) continuous exposure, (B) constant industrial exposure, (C) fluctuating industrial exposure (lognormal distribution GSD= 2.0) (Droz and Wu 1991).

Data in Fig. 1 can be described and analysed using pharmacokinetic techniques. In order to establish a good biological monitoring procedure, many general questions have to be addressed. (1) Looking at variability in Fig. 1 and the added biological contribution, is biological monitoring really much more efficient than personal air monitoring? It can well be that, at least under certain circumstances, air

monitoring gives a better indication of the true exposure of a worker than biological monitoring. (2) Keeping in mind the variability associated with biological data, how many times is it necessary to sample a worker to assess its risk of exposure? (3) Similarly, if the exposure of a group is of interest, how many workers should be monitored? (4) Now in terms of routine monitoring over time, how frequently is it necessary to sample a worker (or a group of workers) in order to be able to detect any change in the exposure conditions? (5) If biological indicator results are so variable, it might well be that this variability indicates differences in risk. Therefore, for which biological indicators would this be true and for what kind of health risks? (6) For chemicals with high rates of penetration through the skin, biological monitoring has an important role to play, and is a much better approach than air monitoring. There are, however, only limited experimental information available for dermal penetration rates. (7) In the case of aerosols of metals, the particle size plays a role in the relationship between biological monitoring data and the exposure. This is also true for the aerosol solubility in the lungs and in the gastrointestinal tract.

Although all these questions can and should be addressed experimentally, a rather efficient approach is to integrate all important parameters in a model framework. This is the principle used in pharmacokinetic modeling. The objective of this presentation is to study the questions described above using pharmacokinetic models of 3 kinds: (1) a simple one-compartment pharmacokinetic model to describe the general behavior of biological indicators, and establish general rules, (2) a physiologically-based pharmacokinetic model which allows the integration of many physiological variables, and (3) a model of dermal uptake.

Methods

One-compartment pharmacokinetic model. The one-compartment pharmacokinetic (OC-PK) model used is described mathematically by the following mass balance equation:

(1) $VdC = K_a C_i dt - K_e C dt$

where V = volume of distribution of the compartment
K_a = first order rate constant for the absorption into the compartment
K_e = first-order rate constant for the elimination out to the compartment
C = Concentration of chemical in the compartment
C_i = concentration of the chemical in inspired air

The half-life $t_{1/2}$ of the chemical in the compartment can be calculated with:

(2) $t_{1/2} = (\ln 2) / K_e$

K_a is a global constant containing the pulmonary ventilation, the retention in the lungs and if there is metabolism, the fraction of the initial chemical described by the OC-PK mode. It can also represent the formation rate of a metabolite from the parent chemical.

Physiologically-based pharmacokinetic model. The physiologically-based pharmacokinetic model (PB-PK) is a 7 compartment model in which the compartments have the following physiological meanings: (1) lungs, (2) muscles and skin, 93) fatty tissues, (4) brain, (5) kidneys, (6) liver and (7) other tissues. Two non-physiological compartments are used to model the pharmacokinetics of 2 potential metabolites (Droz et al. 1989a). This model is flow-limited and therefore can only be used for organic chemicals which permeate very rapidly through membranes. For each compartment, a mass balance equation can be written. For example for tissue i, with volume V_i, blood perfusion Q_i and partition coefficients tissue-gas λ_{ti}:

(3) $V_i \lambda_i dC_i = Q_i \lambda_b C_a dt - Q_i \lambda_b C_i dt$

with C_a = arterial blood concentration of chemical
C_i = venous blood concentration of chemical

For the lung compartment a similar equation can be written, but also including pulmonary ventilation. Metabolism in the liver, and metabolite elimination are described by first-order rate constants.

Individual and exposure variability can be introduced by making some parameters variable: exposure concentration, physical workload (and therefore cardiac output, blood perfusions and pulmonary ventilation), body build, liver function and renal function. In order to simulate groups of workers, these parameters are introduced as a statistical distributions by using Monte-Carlo simulation technics (Droz et al. 1989a).

Dermal uptake model. Dermal uptake can be simulated by making an input into the skin compartment of a PB-PK model, or directly into the single compartment of a OC-PK model. The dermal flux F_d (rate of penetration per unit skin area) is calculated by a two parallel pathway model (polar and lipophilic) (Piscrova-Bergerova et al. 1990). Fd is calculated from water solubility C_{sat}, octanol-water partition coefficient P, and molecular weight MW by:

(4) $F_d = C_{sat} \{0.038 + 0.153\ P\}\ e^{-0.016\ MW\ /\ 15}$

Statistical concepts. Variability in exposure concentration is described by lognormal distributions characterized by their geometric standard deviations (GSD). The corresponding coefficient of variation (CV) can be computed from GSD using the relationship (Droz at al. 1989b):

(5) $CV = [e^{(\ln GSD)^2} - 1]^{1/2}$

Exposure variability is transmitted to the concentration of the chemical in the body according to a transmission factor (variability of the biological levels over that of exposure) which can be calculated for an 8 h industrial exposure by (Rappaport 1991):

(6) $1/\Lambda = (1-e^{-24Ke})\,(1-e^{-16Ke})\,/\,(1-e^{-120Ke})\,(1-e^{-48Ke})^{1/2}$

Variability in biological concentrations of chemicals CV_T is a function of both the variability due to exposure CV_e and the individual biological variability CV_b. Assuming that these 2 contributions are unrelated (Leidel et al. 1977):

(7) $CV_T = [CV_e^{\,2} + CV_b^{\,2}]^{1/2}$

CV_e is itself a function of the exposure GSD and the half-life, through formula (6).

Daily exposures are usually not considered autocorrelated, but biological levels of chemicals can be autocorrelated due to finite rates of elimination. They are described by a first order autoregressive process according to the following model (Droz and Wu 1991):

(8) $Y_t = \mu(1-b_1) + b_1 Y_{t-1} + a$

where Y_t = biological concentration on day t
Y_{t-1} = biological concentration on day t-1
μ = long term mean biological concentration
b_1 = first lag autoregressive coefficient
a = term describing random variations

The autoregressive coefficient is a function of half-life; for the day-to-day autocorrelation:

(9) $b_1 = e^{-(24 \ln 2)/t_{1/2}}$

and for higher lags, for example n days

(10) $b_n = (b_1)^n$

When comparing biological monitoring results with a biological limit value (BLV), it is important to consider confidence intervals. The upper 95% confidence limit (UCL_{95}) and lower confidence limit (LCL_{95}) are calculated with (Leidel et al. 1977):

(11) $UCL_{95} = Y / BLV + 1.645\ CV_T / \sqrt{n}$

(12) $LCL_{95} = Y / BLV - 1.645\ CV_T / \sqrt{n}$

where Y = mean of the biological measurements
BLV = biological limit value such as BEI, BAT or others
n = number of measurements

Analysis of repeated measurements over time can also be carried out using control charts of mean and range (Hawkins and Landenberger 1991).

Results and discussion

Air versus biological monitoring

Biological monitoring has many advantages over air monitoring. Mainly it is an indication of the total dose absorbed, integrating all routes of intake, and specifically dermal uptake. Also it is an elegant tool to assess residual exposure when respiratory protections are worn. However, when those factors are not important, the usefulness of biological monitoring is often questioned. This is especially true when considering the large variability often identified when comparing air and biological monitoring results.

Variability in biological results is due to fluctuations in exposure (characterised by a GSD) and to individual biological variability (characterised by a CVb). Exposure variability is transmitted to the biological concentrations depending on the half-life of the chemical in the body. Therefore, observed variability depends on exposure and biological variability, as well as on the half-life. Fig. 2 presents the estimated number of biological samples which have to be collected in order to test whether exposure is below the acceptable level (Droz and Wu 1991). This is calculated with (Rappaport 1991):

(13) $n = [Z(1 - \alpha) + (1 - \beta)]^2 [s_L^2 + 0.5\ s_b^4] / [(1 - \mu_b) / BLV]^2$

where α = significance level (0.05)
β = statistical power (0.10)
μ_b = true mean of the biological indicator
s_b^2 = variance of the logtransformed biological indicator

In Fig. 2 is also shown the number of air samples required, calculated in the same way; a range of 4 exposure variabilities is considered from a GSD of 1.5 to 3.5. For biological monitoring a median biological variability with $CV_b = 0.3$ is presented together with extreme values of 0.1 and 0.9.

The comparison of the number of samples required for I air and biological monitoring lead to the following comments.

(1) for half-lives below 10 h, there is no statistical advantange in using biological monitoring,
(2) for half-lives greater than 10 h, and with elevated environmental variabilities, there is a definite advantage for biological monitoring, whatever biological variability is considered,
(3) for moderate environmental variabilities, biological monitoring for chemicals with half-lives greater than 10 h is only useful if the biological variability is moderate.

It should also be observed in Fig. 2 that the number of air samples statistically required is rather high, and that in certain circumstances substantial savings can be achieved by using biological monitoring.

Sample size to characterize a worker's or group's exposure

Biological monitoring is often used to assess an exposure situation at a given time, either on an individual basis, or for a group of workers. Due to variability, decisions cannot be made on a single sample. Decision making uses the concept of confidence intervals. Fig. 3 presents what the mean of the measurements should be to be confident at 95% that the true long term exposure is below the BLV, for different sample sizes n (1, 2, 5 and 10). Calculations were done with an exposure GSD of 2.0 and biological variability with CV_b of 0.3 (range 0.1 to 0.9).

As mentioned above, half-life plays an important role. For short half-lives, smaller than 10 h, hardly no decision can be made for long term exposure. Many more samples should be taken. At the other end, with half-lives greater than 500 h, relatively efficient decisions can be taken based on only 1 sample already. Therefore when estimating the long term exposure, biological indicators should be given preference. Some of the disadvantages of biological indicators with short half-lives could be compensated by carrying multisampling.

The same discussion can be carried out for monitoring of groups of workers for their long term exposure. Fig. 4 presents results, calculated in the same way as for a single worker, for groups of 5, 10, 50 and 100 workers. The plots are for decisions made for the mean exposure of the group, and do not guarantee that single workers in the group are not overexposed.

Routine monitoring, how frequent and how many?

One of the main objectives of biological monitoring is the surveillance to confirm that exposure is under control. In other words, biological samples are taken repetitively over time, with the hope that if changes in exposure occur, they will be detected by a careful observation of the data. Control chart technics can be applied in this situation.

The main difficulty here is to separate random fluctuations from fluctuations produced by real changes in exposure. As variability in biological data is a function of the half-life, one can expect that different biological determinants will have different capabilities to detect exposure changes. In fact there are two opposing factors: the longer the biological half-life is, the lower the variability (an advantage), but the longer the half-life, the slower the indicator will respond to a change in exposure, therefore, delaying the indicator of overexposure (a disadvantage). The influence of these factors can be quantified by the use of a OC-PK model, combined with the use of confidence limits. One way to approach this quantitatively is to compare the 95% upper confidence limit (UCL^b_{95}) of the data before the change in exposure, with the lower confidence limit (LCL^a_{95}) after the change.

(14) $UCL^b_{95} = 1 + 1.645\ CV_T / \sqrt{n}$

(15) $LCL^a_{95} = (1 + (C\text{-}1)(1 - e^{-2k_e t})(1 - 1.645\ CV_T / \sqrt{n})$

where n = number of samples or workers in a sampling

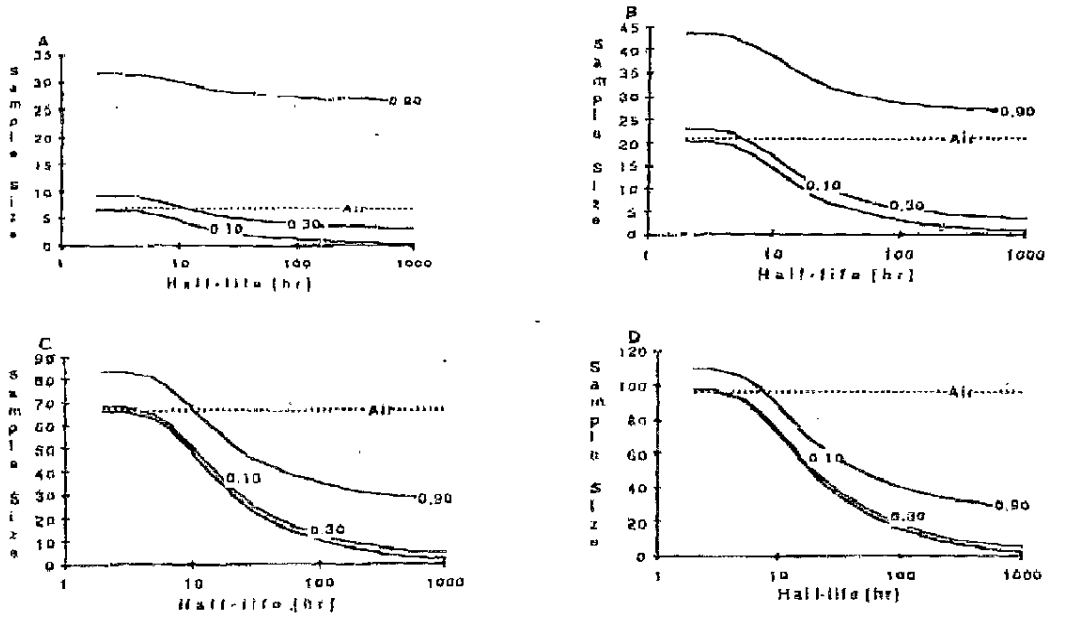

Fig. 2. Predicted biological and air sample size as a function of the half-life for a range of individual variabilities (mean CV 0.30, range 0.10 to 0.90) and different exposure variabilities: (A) GSD 1.5, (B) GSD 2.0, (C) GSD 3.0, (D) GSD 3.5.

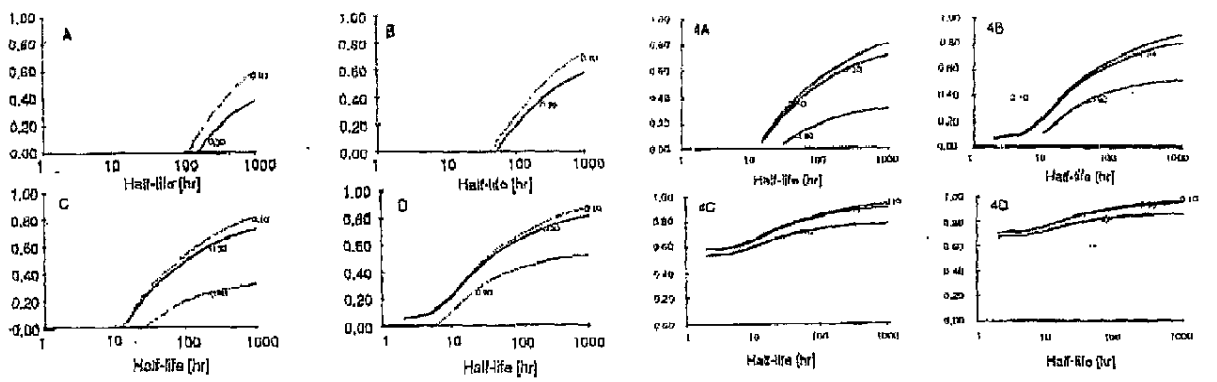

Fig. 3. Predicted ratio - biological measurement to biological limit - (Y-axis) to be confident at 95 % that the true long term biological level is below the limit. Results are shown as a function of the half-life (X-axis) and for a range of individual variabilities (mean CV 0.30, range 0.10 to 0.90), and for an exposure GSD of 2.0. (3A) one sample from a single worker, (3B) 2 samples from a single worker, (3C) 5 samples from a single worker, (3D) 10 samples from a single worker.

Fig. 4. Predicted ratio - biological measurement to biological limit - (Y-axis) to be confident at 95% that the true long term biological level is below the limit. Results are shown as a function of the half-life (X-axis) and for a range of individual variabilities (mean CV 0.30, range 0.10 to 0.90), and for all exposure GSD of 2.0. (4A) group of 5 workers, (4B) of 10 workers, (4C) of 50 workers and (4D) of 100 workers.

Table 1. Range of biological determinants, defined by their biological half-lives, detecting a change of a factor of 2 in exposure.

Frequency***	Biological half-life [h] single worker [samples*] 1	2	3	Group [workers]** 5	10
daily	ns	ns	ns	0-15	0-50
weeky	ns	10-100	5-150	0-200	0-700
monthly	50-150	10-800	5-1000	0-10000	0->1000
quarterly	50-1000	10->1000	6->1000	0->1000	0->1000

* decision made on the mean of 2 or 3 samples
** decision made on the mean of the group of 5 or 10 workers
*** frequency at which biological samples are taken
ns indicates not significant whatever the half-life is

action

CV_T = combined coefficient of variation
t = days between sampling actions
C = change in exposure (after/before)

When the LCL^a_{95} after the change becomes greater than UCL^b_{95} before the change, one can say, for comparison purpose, that at this point the change can be detected. Table 1 presents the results obtained for a change in exposure by a factor of 2. The exposure variability used, both before and after the change, has a GSD of 2.0. Biological variability is considered as medium with a coefficient of variation of 0.30. Five situations are presented: monitoring of a single worker 1, 2 and 3 times, and monitoring of groups of 5 and 10 workers. When several samples are taken, the decision is taken on the mean of the results. Results are presented in terms of half-lives when sampling every day, week, month and quarter.

For example, the application of Table 1 to the case of organic volatiles in blood or breath at the end of the workshift ($t_{1/2}$ 0.5 - 2 h) gives the following information:
(1) this biological monitoring never allows detection of a change in exposure by a factor of 2 for a single worker (with a maximum of 3 samples per sampling action), (2) this method only valid on groups of workers, and at any sampling frequency.
For trichloroethanol in urine at the end of the workshift ($t_{1/2}$ 12 h):
(1) it cannot be used to monitor a single worker based on only one sample, but 2 or 3 samples should be taken and the interpretation done on the mean of the samples,
(2) samples should not be taken more frequently than on a weekly basis,
(3) for groups of 5 to 10 persons, the test (on the group mean) is always significant.
For lead in blood ($t_{1/2}$ 900 h):
(1) single workers can be monitored based on one sample taken every quarter, but not more frequently.
This latter case indicates an interesting property. For biological indicators with long half-lives, sampling should not be done too frequently, as the exposure changes only have a slow and delayed effectes on the indicator.

Indicator of target site concentration or external exposure?

The above discussion was on the relationships between biological indicators and external exposure, assuming that variability has no toxicological implications. In fact variations in biological levels could potentially be related to variations in target doses and therefore to biological effects. The PB-PK model can be used to improve the understanding of the relationships between biological indicators and target doses. Groups of workers having different exposures and individual parameters (body build, liver function, renal function, physical workload) are simulated using Monte Carlo simulation technics. Results are then analysed by linear regressions between the biological indicators and the target dose chosen concentrating on the residual variability which can be described by a coefficient of variation (dispersion around the regression lines) (Droz et al. 1989b). Some results are presented in Fig. 5 for 4 solvents: tetrachloroethylene, trichloroethylene, methylchloroform and styrene. For each solvent relationships between their main biological indicators and the following internal and external exposure concepts were studied: average last day air exposure (TWAD) average last week air exposure (TWAW) total dose absorbed during the last day (ABSD) and the last week (ABSW) average brain concentration of the solvent on the last day (BRAIND indicator of acute CNS health effects) amount of active metabolites formed (BIOWC indicator of metabolism mediated toxicity). The coefficients of variation CV give an idea of the indicator; the smaller the CV, the better the indicator is.

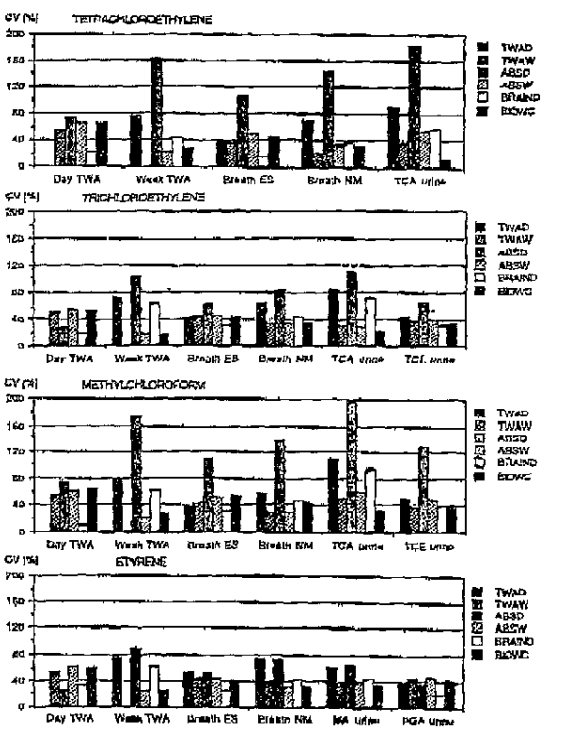

Fig. 5. Comparison of various biological air monitoring indicators as predictors of internal and external exposure. Legend: ES=end of shift, NM=next morning, TCA=trichloroacetic acid, TCE=trichloroethanol, MA=mandelic acid, PGA=phenylglyoxylic acid

Importance of dermal exposure?

Modeling of exposure to industrial chemicals is mainly carried out for inhalation exposure. Nevertheless a large number of chemicals can potentially penetrate into the body through direct contact with the skin. Few experimental data are available to describe this route, and therefore modeling of the penetration flux is of great interest to predict for which chemicals this route is important. Biological monitoring will be of outmost importance for these chemicals. Table 2 presents some examples of flux and amount absorbed through skin under different scenarios (Droz at al. 1991). The amount absorbed by inhalation at the Threshold Limit Value (TLV-TWA) (ACGIH 1991) is also given for comparison.. Bold face means that skin uptake is greater than pulmonary uptake.

Metal aerosols, role of particle size and solubility?

Uptake has been considered as being proportional to exposure concentration for a given chemical, even though retention of course can change with pulmonary ventilation and arterial blood concentration. For metal aerosols, two parameters make the situation different. (1) For the same metal, aerosols can be of different median aerodynamic diameters, depending on the industrial process. This will lead to deposition quantitatively different in the lung regions, and therefore change the absorption pattern. (2) As opposed to organic volatiles, solubilisation of metals in the lungs can be limited, and change from one compound to the other. This will lead in some cases to accumulation in the lung compartment. To illustrate this aspect, a simple pharmacokinetic model is constructed for antimony in Fig. 6. Only 2 compartments are used to describe the lungs: the gas exchange region (GER) from which solubilisation occurs, and the combined

Table 2. Comparative examples of skin and pulmonary absorption

	Flux	TLV	Absorbed per day [mg]			
			lungs	skin		
Chemical	[mg/cm^2/h]	[mg/m^3]	A	B	C	D
Aniline	0.6405	7.6	58.4	**72**	**1152**	**4611**
Biphenyl	0.0759	1.3	9.98	**8.5**	**136**	**546**
o-Cresol	4.5338	22	169	**510**	**8161**	**32643**
Dieldrin	0.0013	0.25	1.92	**0.15**	**2.3**	**9.4**
Dimethylformamide	1.0347	30	230	**116**	**1862**	**7445**
2-Ethoxyethanol	1.2054	18	138	**136**	**2169**	**8679**
Styrene	0.5166	213	1636	**58**	**929**	**3719**
Lindane	0.0087	0.5	3.84	**0.98**	**16**	**62.6**
Methanol	0.1	262	2012	**11**	**180**	**720**
Methyl chloroform	0.87	1910	14669	**98**	**1566**	**6264**
Methylene chloride	0.14	174	1337	**16**	**252**	**1008**

A skveniikar vebtukaruib if 16 l/min and 100% alveolar retention
B infrequent skin exposure: 1 hand (450 cm^2), 15 minutes per day
C frequent skin contact: 2 hands (900 cm^2), 2 h per day
D permanent skin contact: 2 hands (900 cm^2), 8 h per day

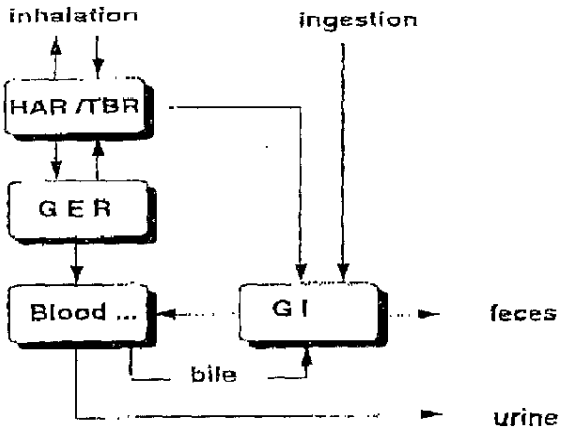

Fig. 6. A simple PB-PK model for antimony with a 2 compartment lung (HAR/TBR head airways and tracheobronchial regions, with respective clearances of 35 h and 72 or 720 h for high and low solubility compounds). Gastro-intestinal absorption is 15%, bilary excretion 90% and urinary excretion half-life 1.5 h.

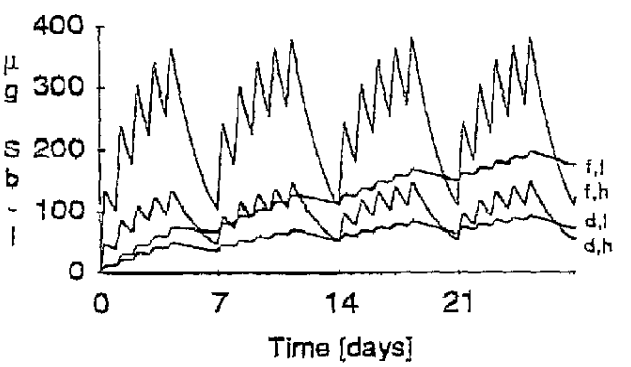

Fig. 7. Urinary antimony concentrations during 4 weeks of industrial exposure to dust (d) and fumes (f) of low (I) and high (II) solubilities. Urine formation rate is 1 ml/min.

head airways (HAR) and tracheobronchial (TBR) regions (Phalen et al. 1986), where clearance is done via the gastrointestinal tract (GI) (Smith 1985). Antimony in the body is distributed into one single compartment, and excreted in the urine (Rees et al. 1980) and in the bile (Bailly et al. 1991). Realistic numbers for the various parameters are shown in Fig. 6.

In order to illustrate the importance of solubility and particle size, simulations were carried out for 4 different situations: exposure to dust (30% respirable) of highly (half-life in GER 72 h) (1) and slightly soluble (720 h) (2) antimony compounds, exposure to fumes (100% respirable) of highly (3) or slightly (4) soluble antimony compounds. The results of urinary excretion obtained are shown in Fig. 7 for a 4 week period of industrial exposure to 500 μg/m^3.

The highest urinary excretions are obtained for exposure to fumes of high solubility, the lowest for dust of low solubility. The curves obtained also show different shapes, the differences between pre- and post-shift samples depend greatly on the physico-chemical characteristics of the aerosol. It is not surprising therefore that relationships between external exposure and urine concentrations vary much from one industrial situation to another. Urine concentrations are a better indicator of systemic dose than of the external exposure. However, lung burden often of interest in the case of exposure to aerosols, is not expected to be very well related to biological levels. It is more likely to be better predicted by air monitoring.

Conclusions

Both simple OC-PK and sophisticated PB-PK models, combined with statistical descriptions and Monte-Carlo simulation technics, have been used in the context of biological monitoring. They are useful to examine the sampling strategies, such as frequency of sampling and number of samples, effect of personal confounding factors such as physical workload and biological variability. The latter parameter is furthermore split into several components with PB-PK population models: body build, liver function, renal function. Aerosols add another degree of complexity because of various particle sizes and solubilities, influencing lung deposition and clearance.

In the context of biological monitoring, OC-PK models leave the advantage of being simple, thus allowing the establishment of general rules on just a few characteristics of the biological indicator. The half-life has been shown to be a very important parameter in establishing sampling strategies.

Limitations of the OC-PK models can be filled by PB-PK models for a more accurate description and when studying the influence of specific physiological and metabolic parameters. Their extension to the aerosols, and more specifically the metals should greatly improve the understanding of their biological monitoring.

Dermal exposure is very frequent in industrial situations and this exposure route should be more often taken into account in modeling for biological monitoring. A simple model exists which allows prediction of penetration rates through the skin. Integration of this approach in OC-PK and PB-PK models should improve the understanding of the influence of skin exposure on biological indicators, and also better target for which chemicals biological monitoring is potentially the most important.

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